JEM

THE
JOURNAL OF
EXPERIMENTAL
MEDICINE

VOLUME 201 NUMBER 1
JANUARY 3, 2005
www.jem.org

ON THE COVER
Artwork (cut Coloraid paper on paper) by New York artist Rachel Urkowitz (email: rachelurk@earthlink.net) representing autoantibodies that cross the placenta and cause congenital heart block in the fetus. Related article by Salomonsson et al.
See page 11

EDITORIAL

1 A new look for 2005
Jennifer Bell and William A. Wells

IN THIS ISSUE

2 Heart-stopping antibodies
Keeping a lid on eosinophil activation
Trouble-making NKT cells
Surviving low oxygen
MBL is good for the heart
Heather L. Van Epps

5 FROM THE ARCHIVE

Discovering lymphocyte subsets
Heather L. Van Epps

COMMENTARIES

7 Do developing B cells need antigen?
Jean-Claude Weill and Claude-Agnès Reynaud

BRIEF DEFINITIVE REPORTS

11 Ro/SSA autoantibodies directly bind cardiomyocytes, disturb calcium homeostasis, and mediate congenital heart block
Stina Salomonsson, Sven-Erik Sonesson, Lars Ottosson, Saad Muhallab, Tomas Olsson, Maria Sunnerhagen, Vijay K. Kuchroo, Peter Thorén, Eric Herlenius, and Marie Wahren-Herlenius See news item on page 2

19 Toll-like receptor 9 mediates innate immune activation by the malaria pigment hemozoin
Cevayir Coban, Ken J. Ishii, Taro Kawai, Hiroaki Hemmi, Shintaro Sato, Satoshi Uematsu, Masahiro Yamamoto, Osamu Takeuchi, Sawako Itagaki, Nirbhay Kumar, Toshihiro Horii, and Shizuo Akira

27 The *Plasmodium* circumsporozoite protein is proteolytically processed during cell invasion
Alida Coppi, Consuelo Pinzon-Ortiz, Christina Hutter, and Photini Sinnis

35 TACI and BAFF-R mediate isotype switching in B cells
Emanuela Castigli, Stephen A. Wilson, Sumi Scott, Fatma Dedeoglu, Shengli Xu, Kong-Peng Lam, Richard J. Bram, Haifa Jabara, and Raif S. Geha

41 NKT cells promote antibody-induced joint inflammation by suppressing transforming growth factor β1 production
Hye Young Kim, Hyun Jung Kim, Hye Sook Min, Sanghee Kim, Weon Seo Park, Seong Hoe Park, and Doo Hyun Chung See news item on page 3

49 **Phosphorylation-dependent translocation of sphingosine kinase to the plasma membrane drives its oncogenic signalling**
Stuart M. Pitson, Pu Xia, Tamara M. Leclercq, Paul A.B. Moretti, Julia R. Zebol, Helen E. Lynn, Binks W. Wattenberg, and Mathew A. Vadas

ARTICLES

55 **Positive selection of the peripheral B cell repertoire in gut-associated lymphoid tissues**
Ki-Jong Rhee, Paul J. Jasper, Periannan Sethupathi, Malathy Shanmugam, Dennis Lanning, and Katherine L. Knight

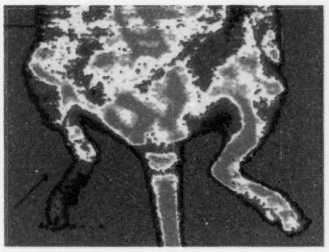
63 **Role of β2-integrins for homing and neovascularization capacity of endothelial progenitor cells**
Emmanouil Chavakis, Alexandra Aicher, Christopher Heeschen, Ken-ichiro Sasaki, Ralf Kaiser, Naual El Makhfi, Carmen Urbich, Thorsten Peters, Karin Scharffetter-Kochanek, Andreas M. Zeiher, Triantafyllos Chavakis, and Stefanie Dimmeler

73 **Spred-1 negatively regulates allergen-induced airway eosinophilia and hyperresponsiveness**
Hiromasa Inoue, Reiko Kato, Satoru Fukuyama, Atsushi Nonami, Kouji Taniguchi, Koichiro Matsumoto, Takako Nakano, Miyuki Tsuda, Mikiko Matsumura, Masato Kubo, Fumihiko Ishikawa, Byoung-gon Moon, Kiyoshi Takatsu, Yoichi Nakanishi, and Akihiko Yoshimura See news item on page 2

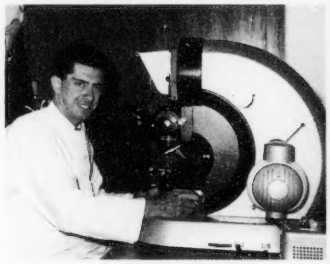
83 **Identification and characterization of an endogenous chemotactic ligand specific for FPRL2**
Isabelle Migeotte, Elena Riboldi, Jean-Denis Franssen, Françoise Grégoire, Cécile Loison, Valérie Wittamer, Michel Detheux, Patrick Robberecht, Sabine Costagliola, Gilbert Vassart, Silvano Sozzani, Marc Parmentier, and David Communi

95 **Identification of poxvirus $CD8^+$ T cell determinants to enable rational design and characterization of smallpox vaccines**
David C. Tscharke, Gunasegaran Karupiah, Jie Zhou, Tara Palmore, Kari R. Irvine, S.M. Mansour Haeryfar, Shanicka Williams, John Sidney, Alessandro Sette, Jack R. Bennink, and Jonathan W. Yewdell

105 **Hypoxia-induced neutrophil survival is mediated by HIF-1α–dependent NF-κB activity**
Sarah R. Walmsley, Cristin Print, Neda Farahi, Carole Peyssonnaux, Randall S. Johnson, Thorsten Cramer, Anastasia Sobolewski, Alison M. Condliffe, Andrew S. Cowburn, Nicola Johnson, and Edwin R. Chilvers See news item on page 3



Homing of endothelial progenitor cells to sites of ischemia (arrow) is impaired in the absence of β2-integrins.
See page 63



Jacques Miller, who identified bone marrow as the source of antibody-producing cells, in his laboratory (1966).
See page 2

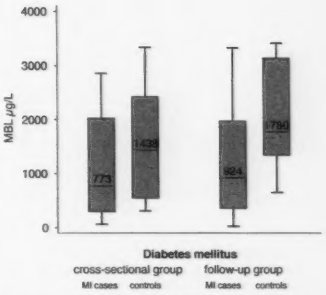
117 **Mannan binding lectin as an adjunct to risk assessment for myocardial infarction in individuals with enhanced risk**
Saedis Saevarsdottir, Oskar Orn Oskarsson, Thor Aspelund, Gudny Eiriksdottir, Thora Vikingsdottir, Vilmundur Gudnason, and Helgi Valdimarsson See news item on page 3

127 **Conversion of $CD4^+$ $CD25^-$ cells into $CD4^+$ $CD25^+$ regulatory T cells in vivo requires B7 costimulation, but not the thymus**
Shuang Liang, Pascale Alard, Yuan Zhao, Sarah Parnell, Sherry L. Clark, and Michele M. Kosiewicz

139 **Synergy of IL-21 and IL-15 in regulating $CD8^+$ T cell expansion and function**
Rong Zeng, Rosanne Spolski, Steven E. Finkelstein, SangKon Oh, Panu E. Kovanen, Christian S. Hinrichs, Cynthia A. Pise-Masison, Michael F. Radonovich, John N. Brady, Nicholas P. Restifo, Jay A. Berzofsky, and Warren J. Leonard

149 **An antagonist peptide mediates positive selection and CD4 lineage commitment of MHC class II–restricted T cells in the absence of CD4**
Henry Kao and Paul M. Allen

159 **Erratum**



Low levels of serum MBL increase risk of myocardial infarction among diabetics.
See page 117

IN THIS ISSUE

162 Surviving rapamycin
DCs redirect T cell traffic
UV-induced T_{reg} cells
Jump-starting tumor-specific T cells
Rethinking EAE pathogenesis
Heather L. Van Epps

NEWS FEATURE

165 Broadening the horizons for yellow fever: new uses for an old vaccine
Heather L. Van Epps

COMMENTARIES

169 IL-12– and IL-23–induced T helper cell subsets: birds of the same feather flock together
Estelle Bettelli and Vijay K. Kuchroo

BRIEF DEFINITIVE REPORTS

173 Prevention of UV radiation–induced immunosuppression by IL-12 is dependent on DNA repair
Agatha Schwarz, Akira Maeda, Kerstin Kernebeck, Harry van Steeg, Stefan Beissert, and Thomas Schwarz See news item on page 162

181 NFATc2 and NFATc3 transcription factors play a crucial role in suppression of $CD4^+$ T lymphocytes by $CD4^+$ $CD25^+$ regulatory T cells
Tobias Bopp, Alois Palmetshofer, Edgar Serfling, Valeska Heib, Steffen Schmitt, Christoph Richter, Matthias Klein, Hansjörg Schild, Edgar Schmitt, and Michael Stassen

189 Impact of DNA ligase IV on nonhomologous end joining pathways during class switch recombination in human cells
Qiang Pan-Hammarström, Anne-Marie Jones, Aleksi Lähdesmäki, Wei Zhou, Richard A. Gatti, Lennart Hammarström, Andrew R. Gennery, and Michael R. Ehrenstein

195 BAFF is produced by astrocytes and up-regulated in multiple sclerosis lesions and primary central nervous system lymphoma
Markus Krumbholz, Diethilde Theil, Tobias Derfuss, Andreas Rosenwald, Frank Schrader, Camelia-Maria Monoranu, Susan L. Kalled, Donna M. Hess, Barbara Serafini, Francesca Aloisi, Hartmut Wekerle, Reinhard Hohlfeld, and Edgar Meinl

JEM

THE JOURNAL OF EXPERIMENTAL MEDICINE

VOLUME 201 NUMBER 2
JANUARY 17, 2005
www.jem.org

ON THE COVER
The diagram illustrates the plasticity of memory T cell recirculation. T cells instructed by local dendritic cells to home to a specific lymphoid site can be redirected by encounter with a dendritic cell from a different site. Related story by Mora et al.
See page 303

ARTICLES

201 **Yellow fever 17D as a vaccine vector for microbial CTL epitopes: protection in a rodent malaria model**
Deng Tao, Giovanna Barba-Spaeth, Urvashi Rai, Victor Nussenzweig, Charles M. Rice, and Ruth S. Nussenzweig

211 **NK cell activation through the NKG2D ligand MULT-1 is selectively prevented by the glycoprotein encoded by mouse cytomegalovirus gene *m145***
Astrid Krmpotic, Milena Hasan, Andrea Loewendorf, Tanja Saulig, Anne Halenius, Tihana Lenac, Bojan Polic, Ivan Bubic, Anja Kriegeskorte, Ester Pernjak-Pugel, Martin Messerle, Hartmut Hengel, Dirk H. Busch, Ulrich H. Koszinowski, and Stipan Jonjic

221 **Dynamic regulation of PU.1 expression in multipotent hematopoietic progenitors**
Stephen L. Nutt, Donald Metcalf, Angela D'Amico, Matthew Polli, and Li Wu

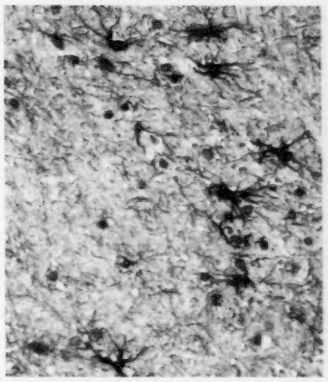
233 **IL-23 drives a pathogenic T cell population that induces autoimmune inflammation**
Claire L. Langrish, Yi Chen, Wendy M. Blumenschein, Jeanine Mattson, Beth Basham, Jonathan D. Sedgwick, Terrill McClanahan, Robert A. Kastelein, and Daniel J. Cua See news item on page 163

241 **High frequency of antitumor T cells in the blood of melanoma patients before and after vaccination with tumor antigens**
Catherine Germeau, Wenbin Ma, Francesca Schiavetti, Christophe Lurquin, Emmanuelle Henry, Nathalie Vigneron, Francis Brasseur, Bernard Lethé, Etienne De Plaen, Thierry Velu, Thierry Boon, and Pierre G. Coulie
See news item on page 163

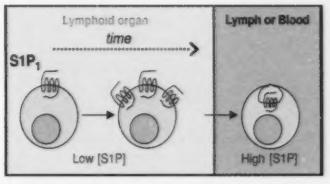
249 **Contrasting frequencies of antitumor and anti-vaccine T cells in metastases of a melanoma patient vaccinated with a MAGE tumor antigen**
Christophe Lurquin, Bernard Lethé, Etienne De Plaen, Véronique Corbière, Ivan Théate, Nicolas van Baren, Pierre G. Coulie, and Thierry Boon
See news item on page 163

259 **The Pim kinases control rapamycin-resistant T cell survival and activation**
Casey J. Fox, Peter S. Hammerman, and Craig B. Thompson
See news item on page 162

267 **Cotranslational endoplasmic reticulum assembly of FcεRI controls the formation of functional IgE-binding receptors**
Edda Fiebiger, Domenico Tortorella, Marie-Helene Jouvin, Jean-Pierre Kinet, and Hidde L. Ploegh



B cell–activating factor of the TNF family (BAFF) is expressed on astrocytes (dark brown) and is increased in lesions of multiple sclerosis patients.
See page 195



Sphingosine-1-phosphate receptor 1 ($S1P_1$) is downregulated on lymphocytes circulating in the blood and lymph and upregulated as cells transit through lymphoid tissues.
See page 291

279 **Essential role of p53 phosphorylation by p38 MAPK in apoptosis induction by the HIV-1 envelope**
Jean-Luc Perfettini, Maria Castedo, Roberta Nardacci, Fabiola Ciccosanti, Patricia Boya, Thomas Roumier, Nathanael Larochette, Mauro Piacentini, and Guido Kroemer

291 **Cyclical modulation of sphingosine-1-phosphate receptor 1 surface expression during lymphocyte recirculation and relationship to lymphoid organ transit**
Charles G. Lo, Ying Xu, Richard L. Proia, and Jason G. Cyster

303 **Reciprocal and dynamic control of CD8 T cell homing by dendritic cells from skin- and gut-associated lymphoid tissues**
J. Rodrigo Mora, Guiying Cheng, Dominic Picarella, Michael Briskin, Natasha Buchanan, and Ulrich H. von Andrian See news item on page 162

HIV-1 envelope–driven apoptosis requires activated p38 MAP kinase (MAPK) (red), which phosphorylates and activates proapoptotic protein p53.
See page 279

IN MEMORIAM

317 Maclyn McCarty (1911–2005)
The Editors, *The Journal of Experimental Medicine*

IN THIS ISSUE

318 Controlling RAGE
MIC1 and MIC3: partners in invasion
DOKing TLR4 signals
LSP1: gatekeeper of the endothelium
Cancer-causing motifs
Heather L. Van Epps

FROM THE ARCHIVE

320 Peyton Rous: father of the tumor virus
Heather L. Van Epps

COMMENTARIES

321 Bacterial toxins and the immune system: show me the in vivo targets
Jorge E. Galán

BRIEF DEFINITIVE REPORTS

325 Anthrax toxins suppress T lymphocyte activation by disrupting antigen receptor signaling
Silvia Rossi Paccani, Fiorella Tonello, Raffaella Ghittoni, Mariarita Natale, Lucia Muraro, Mario Milco D'Elios, Wei-Jen Tang, Cesare Montecucco, and Cosima T. Baldari
See commentary on page 321

333 Dok-1 and Dok-2 are negative regulators of lipopolysaccharide-induced signaling
Hisaaki Shinohara, Akane Inoue, Noriko Toyama-Sorimachi, Yoshinori Nagai, Tomoharu Yasuda, Hiromi Suzuki, Reiko Horai, Yoichiro Iwakura, Tadashi Yamamoto, Hajime Karasuyama, Kensuke Miyake, and Yuji Yamanashi
See news item on page 318

341 Direct in vivo V_H to J_H rearrangement violating the 12/23 rule
Sergei B. Koralov, Tatiana I. Novobrantseva, Konrad Hochedlinger, Rudolf Jaenisch, and Klaus Rajewsky

JEM

THE JOURNAL OF EXPERIMENTAL MEDICINE

VOLUME 201 NUMBER 3
FEBRUARY 7, 2005
www.jem.org

ON THE COVER
The image shows *Toxoplasma gondii* parasites stained with a polyclonal antibody specific for the microneme protein MIC3 (red). Related story by Cérède et al.
See page 453

ARTICLES

349 **$CD8^+$ immunodominance among Epstein-Barr virus lytic cycle antigens directly reflects the efficiency of antigen presentation in lytically infected cells**
Victoria A. Pudney, Alison M. Leese, Alan B. Rickinson, and Andrew D. Hislop

361 **The adaptor molecules LAT and SLP-76 are specifically targeted by *Yersinia* to inhibit T cell activation**
Christiane Gerke, Stanley Falkow, and Yueh-hsiu Chien
See commentary on page 321

373 **Plasmacytoid precursor dendritic cells facilitate allogeneic hematopoietic stem cell engraftment**
Isabelle J. Fugier-Vivier, Francine Rezzoug, Yiming Huang, Amanda J. Graul-Layman, Carrie L. Schanie, Hong Xu, Paula M. Chilton, and Suzanne T. Ildstad

385 **Anti-CD63 antibodies suppress IgE-dependent allergic reactions in vitro and in vivo**
Stefan Kraft, Tony Fleming, James M. Billingsley, Shih-Yao Lin, Marie-Hélène Jouvin, Peter Storz, and Jean-Pierre Kinet

397 **Regulation of T helper type 2 cell differentiation by murine Schnurri-2**
Motoko Y. Kimura, Hiroyuki Hosokawa, Masakatsu Yamashita, Akihiro Hasegawa, Chiaki Iwamura, Hiroshi Watarai, Masaru Taniguchi, Tsuyoshi Takagi, Shunsuke Ishii, and Toshinori Nakayama

409 **LSP1 is an endothelial gatekeeper of leukocyte transendothelial migration**
Lixin Liu, Denise C. Cara, Jaswinder Kaur, Eko Raharjo, Sarah C. Mullaly, Jenny Jongstra-Bilen, Jan Jongstra, and Paul Kubes
See news item on page 319

419 **Dlgh1 coordinates actin polymerization, synaptic T cell receptor and lipid raft aggregation, and effector function in T cells**
June L. Round, Tamar Tomassian, Min Zhang, Viresh Patel, Stephen P. Schoenberger, and M. Carrie Miceli

431 **MMTV Env encodes an ITAM responsible for transformation of mammary epithelial cells in three-dimensional culture**
Elad Katz, Mohamed H. Lareef, John C. Rassa, Shannon M. Grande, Leslie B. King, Jose Russo, Susan R. Ross, and John G. Monroe
See news item on page 319

Peyton Rous, the father of tumor viruses, at his microscope in 1923.
See page 320

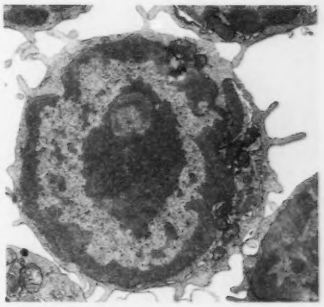
Crystal structure of the cytoplasmic region of the tyrosine phosphatase CD45 sheds new light on its mechanism of action.
See page 441

441 **Structural basis for the function and regulation of the receptor protein tyrosine phosphatase CD45**
Hyun-Joo Nam, Florence Poy, Haruo Saito, and Christin A. Frederick

453 **Synergistic role of micronemal proteins in *Toxoplasma gondii* virulence**
Odile Cérède, Jean François Dubremetz, Martine Soête, Didier Deslée, Henri Vial, Daniel Bout, and Maryse Lebrun
See news item on page 318

465 **Direct cleavage of ROCK II by granzyme B induces target cell membrane blebbing in a caspase-independent manner**
Michael Sebbagh, Jocelyne Hamelin, Jacques Bertoglio, Eric Solary, and Jacqueline Bréard

473 **RAGE limits regeneration after massive liver injury by coordinated suppression of TNF-α and NF-κB**
Guellue Cataldegirmen, Shan Zeng, Nikki Feirt, Nikalesh Ippagunta, Hao Dun, Wu Qu, Yan Lu, Ling Ling Rong, Marion A. Hofmann, Thomas Kislinger, Sophia I. Pachydaki, Daniel G. Jenkins, Alan Weinberg, Jay Lefkowitch, Xavier Rogiers, Shi Fang Yan, Ann Marie Schmidt, and Jean C. Emond
See news item on page 318



Plasmacytoid precursor dendritic cells enhance engraftment of hematopoietic stem cells in allograft recipients without causing graft versus host disease.
See page 373

IN THIS ISSUE

486 Pollen polarize dendritic cells
Signaling survival
Muscle cells under attack
Phagocytosis without inflammation
Heather L. Van Epps

COMMENTARIES

489 Twisting tails exposed: the evidence for TCR conformational change
Susan E. Levin and Arthur Weiss

493 Identifying protein–protein interactions in somatic hypermutation
Myron F. Goodman and Matthew D. Scharff

497 Selecting B cells and plasma cells to memory
Thomas Dörner and Andreas Radbruch

501 Movies, measurement, and modeling: the three Ms of mechanistic immunology
Colleen Witt, Subhadip Raychaudhuri, and Arup K. Chakraborty

DISCUSSION

505 On imaging, speed, and the future of lymphocyte signaling
Alexander Tarakhovsky

See commentary on page 501

BRIEF DEFINITIVE REPORTS

509 Role of ChemR23 in directing the migration of myeloid and plasmacytoid dendritic cells to lymphoid organs and inflamed skin
William Vermi, Elena Riboldi, Valerie Wittamer, Francesca Gentili, Walter Luini, Simona Marrelli, Annunciata Vecchi, Jean-Denis Franssen, David Communi, Luisa Massardi, Marina Sironi, Alberto Mantovani, Marc Parmentier, Fabio Facchetti, and Silvano Sozzani

517 T cell receptor engagement by peptide–MHC ligands induces a conformational change in the CD3 complex of thymocytes
Diana Gil, Adam G. Schrum, Balbino Alarcón, and Ed Palmer

See commentary on page 489

JEM

THE
JOURNAL OF
EXPERIMENTAL
MEDICINE

VOLUME 201 NUMBER 4
FEBRUARY 21, 2005
www.jem.org

ON THE COVER
The image shows false-color electron micrographs of birch tree pollen, which trigger allergic T helper 2 responses by inhibiting interleukin-12 production by dendritic cells. Electron micrographs were prepared with the assistance of Ingrid Weichenmeier (Technische Universität München, Munich, Germany). Related article by Traidl-Hoffmann et al.
See page 627

ARTICLES

523 **Private specificities of CD8 T cell responses control patterns of heterologous immunity**
Sung-Kwon Kim, Markus Cornberg, Xiaoting Z. Wang, Hong D. Chen, Liisa K. Selin, and Raymond M. Welsh

535 ***Mycobacterium tuberculosis* controls host innate immune activation through cyclopropane modification of a glycolipid effector molecule**
Vivek Rao, Nagatoshi Fujiwara, Steven A. Porcelli, and Michael S. Glickman

545 **Early appearance of germinal center–derived memory B cells and plasma cells in blood after primary immunization**
Elizabeth J. Blink, Amanda Light, Axel Kallies, Stephen L. Nutt, Philip D. Hodgkin, and David M. Tarlinton
See commentary on page 497

555 **An orderly inactivation of intracellular retention signals controls surface expression of the T cell antigen receptor**
Pilar Delgado and Balbino Alarcón

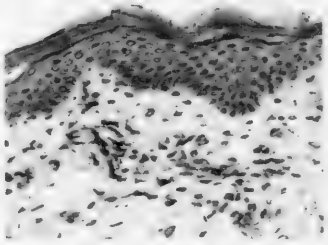
567 **The complement inhibitory protein DAF (CD55) suppresses T cell immunity in vivo**
Jianuo Liu, Takashi Miwa, Brendan Hilliard, Youhai Chen, John D. Lambris, Andrew D. Wells, and Wen-Chao Song

579 **Lineage relationships, homeostasis, and recall capacities of central– and effector–memory CD8 T cells in vivo**
Cécile Bouneaud, Zacarias Garcia, Philippe Kourilsky, and Christophe Pannetier

591 **Enhanced autoantigen expression in regenerating muscle cells in idiopathic inflammatory myopathy**
Livia Casciola-Rosen, Kanneboyina Nagaraju, Paul Plotz, Kondi Wang, Stuart Levine, Edward Gabrielson, Andrea Corse, and Antony Rosen
See news item on page 487

603 **The BCL2A1 gene as a pre–T cell receptor–induced regulator of thymocyte survival**
Malay Mandal, Christine Borowski, Teresa Palomero, Adolfo A. Ferrando, Philipp Oberdoerffer, Fanyong Meng, Antonio Ruiz-Vela, Maria Ciofani, Juan-Carlos Zuniga-Pflucker, Isabella Screpanti, A. Thomas Look, Stanley J. Korsmeyer, Klaus Rajewsky, Harald von Boehmer, and Iannis Aifantis
See news item on page 486

615 **Ets-1, a functional cofactor of T-bet, is essential for Th1 inflammatory responses**
Roland Grenningloh, Bok Yun Kang, and I-Cheng Ho



Plasmacytoid dendritic cells in the skin express ChemR23 (brown), the receptor for the chemotactic molecule chimerin.
See page 509

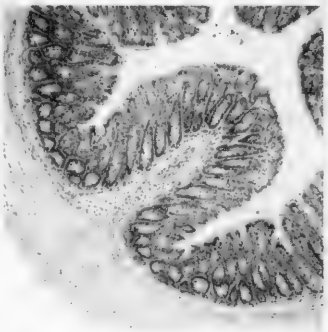
ER retention signals must be inactivated in a step-wise fashion for the complete TCR–CD3 complex to be expressed.
See page 555

627 **Pollen-associated phytoprostanes inhibit dendritic cell interleukin-12 production and augment T helper type 2 cell polarization**
Claudia Traidl-Hoffmann, Valentina Mariani, Hubertus Hochrein, Kathrin Karg, Hermann Wagner, Johannes Ring, Martin J. Mueller, Thilo Jakob, and Heidrun Behrendt
See news item on page 486

637 **MSH2–MSH6 stimulates DNA polymerase η, suggesting a role for A:T mutations in antibody genes**
Teresa M. Wilson, Alexandra Vaisman, Stella A. Martomo, Patsa Sullivan, Li Lan, Fumio Hanaoka, Akira Yasui, Roger Woodgate, and Patricia J. Gearhart
See commentary on page 493

647 **Clearance of apoptotic neurons without inflammation by microglial triggering receptor expressed on myeloid cells-2**
Kazuya Takahashi, Christian D.P. Rochford, and Harald Neumann
See news item on page 487

659 **Erratum**



Mice lacking the transcription factor Ets-1 are protected against Th1-driven intestinal colitis.
See page 615

JEM
THE JOURNAL OF EXPERIMENTAL MEDICINE
VOLUME 201 NUMBER 5
MARCH 7, 2005
www.jem.org

IN THIS ISSUE

662 Inflammation control gets fishy
NKT cells depend on SAP
Out with the old, in with the new
Refusing to be suppressed
Heather L. Van Epps

FROM THE ARCHIVE

665 Rules of engagement: the discovery of MHC restriction
Heather L. Van Epps

COMMENTARIES

667 Private aspects of heterologous immunity
Barbara Rehermann and Eui-Cheol Shin

671 Controlling inflammation: a fat chance?
Roderick J. Flower and Mauro Perretti

BRIEF DEFINITIVE REPORTS

675 Heterologous T cell immunity in severe hepatitis C virus infection
Simona Urbani, Barbara Amadei, Paola Fisicaro, Massimo Pilli, Gabriele Missale, Antonio Bertoletti, and Carlo Ferrari
See commentary on page 667

681 Definition of target antigens for naturally occurring $CD4^+$ $CD25^+$ regulatory T cells
Hiroyoshi Nishikawa, Takuma Kato, Isao Tawara, Kanako Saito, Hiroaki Ikeda, Kagemasa Kuribayashi, Paul M. Allen, Robert D. Schreiber, Shimon Sakaguchi, Lloyd J. Old, and Hiroshi Shiku

687 Presence of osteoclast-like multinucleated giant cells in the bone and nonostotic lesions of Langerhans cell histiocytosis
Cristiana E.T. da Costa, Nicola E. Annels, Claudia M.J.M. Faaij, Ramses G. Forsyth, Pancras C.W. Hogendoorn, and R. Maarten Egeler

695 Defective NKT cell development in mice and humans lacking the adapter SAP, the X-linked lymphoproliferative syndrome gene product
Benoit Pasquier, Luo Yin, Marie-Claude Fondanèche, Francis Relouzat, Coralie Bloch-Queyrat, Nathalie Lambert, Alain Fischer, Geneviève de Saint-Basile, and Sylvain Latour
See news item on page 662

ON THE COVER
The image shows the structure of human resolvin E1, an antiinflammatory lipid derived from essential fatty acids in fish oils, which mediates its effects through the G protein–coupled receptor ChemR23. Related article by Arita et al.
See page 713

ARTICLES

703 **Defective B cell tolerance checkpoints in systemic lupus erythematosus**
Sergey Yurasov, Hedda Wardemann, Johanna Hammersen, Makoto Tsuiji, Eric Meffre, Virginia Pascual, and Michel C. Nussenzweig

713 **Stereochemical assignment, antiinflammatory properties, and receptor for the omega-3 lipid mediator resolvin E1**
Makoto Arita, Francesca Bianchini, Julio Aliberti, Alan Sher, Nan Chiang, Song Hong, Rong Yang, Nicos A. Petasis, and Charles N. Serhan
See commentary on page 671
See news item on page 662

723 **Homeostatic maintenance of natural *Foxp3*$^+$ CD25$^+$ CD4$^+$ regulatory T cells by interleukin (IL)-2 and induction of autoimmune disease by IL-2 neutralization**
Ruka Setoguchi, Shohei Hori, Takeshi Takahashi, and Shimon Sakaguchi

737 **T cells that cannot respond to TGF-β escape control by CD4$^+$CD25$^+$ regulatory T cells**
Linda Fahlén, Simon Read, Leonid Gorelik, Stephen D. Hurst, Robert L. Coffman, Richard A. Flavell, and Fiona Powrie
See news item on page 663

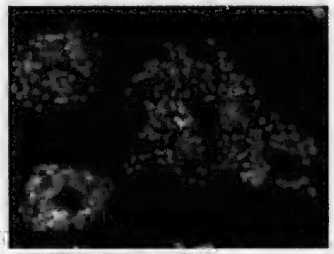
747 **A role for IgG immune complexes during infection with the intracellular pathogen *Leishmania***
Suzanne A. Miles, Sean M. Conrad, Renata G. Alves, Selma M.B. Jeronimo, and David M. Mosser

755 **Mycobacterial catalase–peroxidase is a tissue antigen and target of the adaptive immune response in systemic sarcoidosis**
Zhimin Song, Lisa Marzilli, Brian M. Greenlee, Edward S. Chen, Richard F. Silver, Frederic B. Askin, Alvin S. Teirstein, Ying Zhang, Robert J. Cotter, and David R. Moller

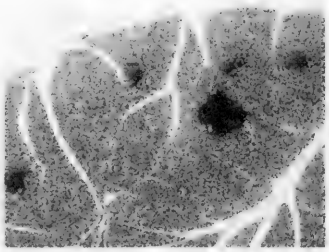
769 **Essential role for interleukin-2 for CD4$^+$CD25$^+$ T regulatory cell development during the neonatal period**
Allison L. Bayer, Aixin Yu, Dennis Adeegbe, and Thomas R. Malek

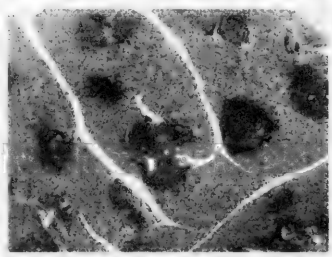
779 **Intratumor depletion of CD4$^+$ cells unmasks tumor immunogenicity leading to the rejection of late-stage tumors**
Ping Yu, Youjin Lee, Wenhua Liu, Thomas Krausz, Anita Chong, Hans Schreiber, and Yang-Xin Fu

793 **Phosphorylation of histone deacetylase 7 by protein kinase D mediates T cell receptor–induced Nur77 expression and apoptosis**
Franck Dequiedt, Johan Van Lint, Emily Lecomte, Viktor Van Duppen, Thomas Seufferlein, Jackie R. Vandenheede, Ruddy Wattiez, and Richard Kettmann



Specific IgG antibodies (green) bind to *Leishmania major* amastigotes (shown inside macrophages) and exacerbate disease.
See page 747





Neutralization of IL-2 (bottom panel) accelerates diabetes in NOD mice due to a reduction in regulatory T cells.
See page 723

805 **Thymic output generates a new and diverse TCR repertoire after autologous stem cell transplantation in multiple sclerosis patients**
Paolo A. Muraro, Daniel C. Douek, Amy Packer, Katherine Chung, Francisco J. Guenaga, Riccardo Cassiani-Ingoni, Catherine Campbell, Sarfraz Memon, James W. Nagle, Frances T. Hakim, Ronald E. Gress, Henry F. McFarland, Richard K. Burt, and Roland Martin
See news item on page 663

817 **An immunoglobulin Cκ-reactive single chain antibody fusion protein induces tolerance through receptor editing in a normal polyclonal immune system**
Djemel Ait-Azzouzene, Laurent Verkoczy, Jorieke Peters, Amanda Gavin, Patrick Skog, José Luis Vela, and David Nemazee

Multinucleated giant cells in bone lesions of patients with langerhans cell histiocytosis express osteoclast markers CD68 (blue) and matrix metalloprotease-9 (red).
See page 687

JEM
THE JOURNAL OF EXPERIMENTAL MEDICINE
VOLUME 201 NUMBER 6
MARCH 21, 2005
www.jem.org

IN THIS ISSUE

830 Two strikes lead to leukemia
Defenseless against the common cold
Too old to help
Clean living staves off autoimmunity
Heather L. Van Epps

COMMENTARIES

833 Signaling for NKT cell development: the SAP–FynT connection
Christine Borowski and Albert Bendelac

837 T cell aging: naive but not young
Janko Nikolich-Žugich

841 Identifying genes that regulate bone remodeling as potential therapeutic targets
Stephen M. Krane

BRIEF DEFINITIVE REPORTS

845 Newly generated CD4 T cells in aged animals do not exhibit age-related defects in response to antigen
Laura Haynes, Sheri M. Eaton, Eve M. Burns, Troy D. Randall, and Susan L. Swain
See commentary on page 837
See news article on page 831

853 Granulocyte/macrophage colony-stimulating factor and accessory cells modulate radioprotection by purified hematopoietic cells
Tamiko R. Katsumoto, Jennifer Duda, Andrew Kim, Zabihullah Wardak, Glenn Dranoff, D. Wade Clapp, and Kevin Shannon

ARTICLES

859 Regulation of anaphylactic responses by phosphatidylinositol phosphate kinase type I α
Junko Sasaki, Takehiko Sasaki, Masakazu Yamazaki, Kunie Matsuoka, Choji Taya, Hiroshi Shitara, Shunsuke Takasuga, Miki Nishio, Katsunori Mizuno, Teiji Wada, Hideyuki Miyazaki, Hiroshi Watanabe, Ryota Iizuka, Shuichi Kubo, Shigeo Murata, Tomoki Chiba, Tomohiko Maehama, Koichi Hamada, Hiroyuki Kishimoto, Michael A. Frohman, Keiji Tanaka, Josef M. Penninger, Hiromichi Yonekawa, Akira Suzuki, and Yasunori Kanaho

871 Platelet activation leads to activation and propagation of the complement system
Ian del Conde, Miguel A. Crúz, Hui Zhang, José A. López, and Vahid Afshar-Kharghan

ON THE COVER
The image is a micrograph (false color) showing myeloproliferation in the spleen of leukemia-prone BHX-2 mice. Related article by Turcotte et al.
See page 881

881 **A mutation in the *Icsbp1* gene causes susceptibility to infection and a chronic myeloid leukemia–like syndrome in BXH-2 mice**
Karine Turcotte, Susan Gauthier, Ashleigh Tuite, Alaka Mullick, Danielle Malo, and Philippe Gros
See news article on page 830

891 **Transmission and accumulation of CTL escape variants drive negative associations between HIV polymorphisms and HLA**
Alasdair Leslie, Daniel Kavanagh, Isobella Honeyborne, Katja Pfafferott, Charles Edwards, Tilly Pillay, Louise Hilton, Christina Thobakgale, Danni Ramduth, Rika Draenert, Sylvie Le Gall, Graz Luzzi, Anne Edwards, Christian Brander, Andrew K. Sewell, Sarah Moore, James Mullins, Corey Moore, Simon Mallal, Nina Bhardwaj, Karina Yusim, Rodney Phillips, Paul Klenerman, Bette Korber, Photini Kiepiela, Bruce Walker, and Philip Goulder

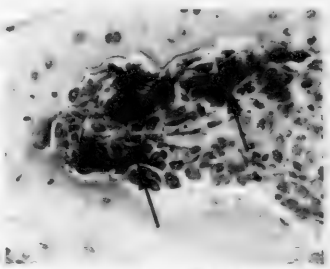
903 **CD44 is a determinant of inflammatory bone loss**
Silvia Hayer, Günter Steiner, Birgit Görtz, Erika Reiter, Makiyeh Tohidast-Akrad, Michael Amling, Oskar Hoffmann, Kurt Redlich, Jochen Zwerina, Karl Skriner, Frank Hilberg, Erwin F. Wagner, Josef S. Smolen, and Georg Schett

915 **Interleukin-1 receptor-associated kinase-1 plays an essential role for Toll-like receptor (TLR)7- and TLR9-mediated interferon-α induction**
Satoshi Uematsu, Shintaro Sato, Masahiro Yamamoto, Tomonori Hirotani, Hiroki Kato, Fumihiko Takeshita, Michiyuki Matsuda, Cevayir Coban, Ken J Ishii, Taro Kawai, Osamu Takeuchi, and Shizuo Akira

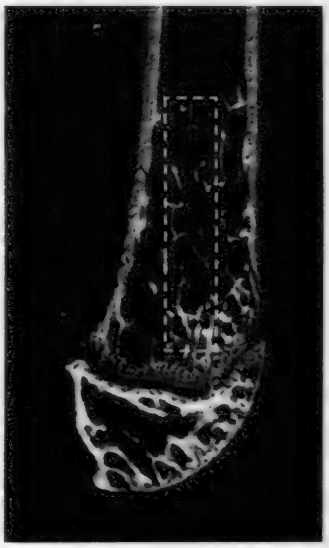
925 **Inhibition of platelet-derived growth factor signaling attenuates pulmonary fibrosis**
Amir Abdollahi, Minglun Li, Gong Ping, Christian Plathow, Sophie Domhan, Fabian Kiessling, Leslie B. Lee, Gerald McMahon, Hermann-Josef Gröne, Kenneth E. Lipson, and Peter E. Huber

937 **Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus**
Peter A.B. Wark, Sebastian L. Johnston, Fabio Bucchieri, Robert Powell, Sarah Puddicombe, Vasile Laza-Stanca, Stephen T. Holgate, and Donna E. Davies
See news article on page 830

949 **A role for fungal β-glucans and their receptor Dectin-1 in the induction of autoimmune arthritis in genetically susceptible mice**
Hiroyuki Yoshitomi, Noriko Sakaguchi, Katsuya Kobayashi, Gordon D. Brown, Tomoyuki Tagami, Toshiko Sakihama, Keiji Hirota, Satoshi Tanaka, Takashi Nomura, Ichiro Miki, Siamon Gordon, Shizuo Akira, Takashi Nakamura, and Shimon Sakaguchi
See news article on page 831



Absence of CD44 results in increased numbers of osteoclasts (purple) in joints and increased bone destruction during inflammation-induced arthritis.
See page 903



The focal adhesion protein CIZ is a negative regulator of osteoclast function—its absence causes increased bone mass.
See page 961

961 The nucleocytoplasmic shuttling protein CIZ reduces adult bone mass by inhibiting bone morphogenetic protein–induced bone formation
Mikihiko Morinobu, Tetsuya Nakamoto, Kazunori Hino, Kunikazu Tsuji, Zhong-Jian Shen, Kazuhisa Nakashima, Akira Nifuji, Haruyasu Yamamoto, Hisamaru Hirai, and Masaki Noda
See commentary on page 841

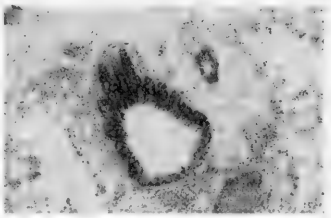
971 Interleukin-7 is necessary to maintain the B cell potential in common lymphoid progenitors
Sheila Dias, Hamilton Silva Jr., Ana Cumano, and Paulo Vieira

981 In vivo depletion of lung CD11c^{+} dendritic cells during allergen challenge abrogates the characteristic features of asthma
Leonie S. van Rijt, Steffen Jung, Alex KleinJan, Nanda Vos, Monique Willart, Catherine Duez, Henk C. Hoogsteden, and Bart N. Lambrecht

993 Complement receptors regulate differentiation of bone marrow plasma cell precursors expressing transcription factors Blimp-1 and XBP-1
Dominique Gatto, Thomas Pfister, Andrea Jegerlehner, Stephen W. Martin, Manfred Kopf, and Martin F. Bachmann

1007 Vaccinia virus protein A46R targets multiple Toll-like–interleukin-1 receptor adaptors and contributes to virulence
Julianne Stack, Ismar R. Haga, Martina Schröder, Nathan W. Bartlett, Geraldine Maloney, Patrick C. Reading, Katherine A. Fitzgerald, Geoffrey L. Smith, and Andrew G. Bowie

1019 Correction



Dendritic cells are required for the development of allergic asthma.
See page 981

JEM
THE JOURNAL OF EXPERIMENTAL MEDICINE
VOLUME 201 NUMBER 7
APRIL 4, 2005
www.jem.org

IN THIS ISSUE

1022 Paving the way to metastasis
Killer combinations for cervical cancer
Controlling unruly osteoclasts
Overstimulated and ineffective
The way to the skin
Heather L. Van Epps

FROM THE ARCHIVE

1024 What tumors need: a brief history of angiogenesis
Heather L. Van Epps

COMMENTARIES

1025 Understanding how combinations of HLA and KIR genes influence disease
Sumati Rajagopalan and Eric O. Long

BRIEF DEFINITIVE REPORTS

1031 Protection from cytomegalovirus after transplantation is correlated with immediate early 1–specific CD8 T cells
Torsten Bunde, Alexander Kirchner, Bodo Hoffmeister, Dirk Habedank, Roland Hetzer, Georgy Cherepnev, Susanna Proesch, Petra Reinke, Hans-Dieter Volk, Hans Lehmkuhl, and Florian Kern

1037 Recruitment of Foxp3$^+$ T regulatory cells mediating allograft tolerance depends on the CCR4 chemokine receptor
Iris Lee, Liqing Wang, Andrew D. Wells, Martin E. Dorf, Engin Ozkaynak, and Wayne W. Hancock

1045 A role for CCR4 in development of mature circulating cutaneous T helper memory cell populations
Espen S. Baekkevold, Marc-André Wurbel, Pia Kivisäkk, Clare M. Wain, Christine A. Power, Guttorm Haraldsen, and James J. Campbel
See news article on page 1023

1053 Interferon-γ acts directly on CD8$^+$ T cells to increase their abundance during virus infection
Jason K. Whitmire, Joyce T. Tan, and J. Lindsay Whitton

1061 TGF-β1 maintains suppressor function and Foxp3 expression in CD4$^+$CD25$^+$ regulatory T cells
Julien C. Marie, John J. Letterio, Marc Gavin, and Alexander Y. Rudensky

ON THE COVER
The image shows increased growth of lymphatic vessels (red) and blood vessels (green) in skin tumors expressing vascular endothelial growth factor A (VEGF-A). Related article by Hirakawa et al.
See page 1089

1069 **Hierarchy of resistance to cervical neoplasia mediated by combinations of killer immunoglobulin-like receptor and human leukocyte antigen loci**
Mary Carrington, Sophia Wang, Maureen P. Martin, Xiaojiang Gao, Mark Schiffman, Jie Cheng, Rolando Herrero, Ana Cecilia Rodriguez, Robert Kurman, Rodrigue Mortel, Peter Schwartz, Andrew Glass, and Allan Hildesheim
See commentary on page 1025
See news article on page 1022

The nuclear factor HMGB1 (red) mediates inflammation and liver damage during ischemia-reperfusion injury.
See page 1135

ARTICLES

1077 **Serine protease inhibitors serpina1 and serpina3 are down-regulated in bone marrow during hematopoietic progenitor mobilization**
Ingrid G. Winkler, Jean Hendy, Paul Coughlin, Anita Horvath, and Jean-Pierre Lévesque

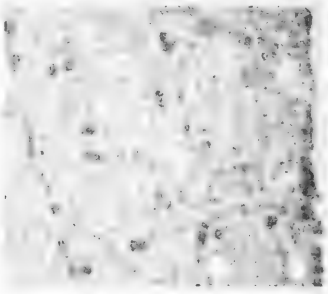
1089 **VEGF-A induces tumor and sentinel lymph node lymphangiogenesis and promotes lymphatic metastasis**
Satoshi Hirakawa, Shohta Kodama, Rainer Kunstfeld, Kentaro Kajiya, Lawrence F. Brown, and Michael Detmar
See news article on page 1022

1101 **Repeated stimulation of CD4 effector T cells can limit their protective function**
Dawn M. Jelley-Gibbs, John P. Dibble, Svetlana Filipson, Laura Haynes, Roslyn A. Kemp, and Susan L. Swain
See news article on page 1023

1113 **Cholinergic stimulation blocks endothelial cell activation and leukocyte recruitment during inflammation**
Rubina W. Saeed, Santosh Varma, Tina Peng-Nemeroff, Barbara Sherry, David Balakhaneh, Jared Huston, Kevin J. Tracey, Yousef Al-Abed, and Christine N. Metz

1125 **Mutation of the phospholipase C-γ1–binding site of LAT affects both positive and negative thymocyte selection**
Connie L. Sommers, Jan Lee, Kevin L. Steiner, Jordan M. Gurson, Corinne L. DePersis, Dalal El-Khoury, Claudette L. Fuller, Elizabeth W. Shores, Paul E. Love, and Lawrence E. Samelson

1135 **The nuclear factor HMGB1 mediates hepatic injury after murine liver ischemia-reperfusion**
Allan Tsung, Rohit Sahai, Hiroyuki Tanaka, Atsunori Nakao, Mitchell P. Fink, Michael T. Lotze, Huan Yang, Jianhua Li, Kevin J. Tracey, David A. Geller, and Timothy R. Billiar

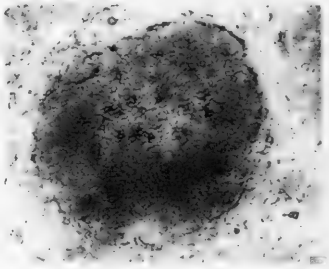


Serine protease inhibitor serpina 1 (brown) is down-regulated in the bone marrow during mobilization of hematopoietic progenitor cells.
See page 1077

1145 **Natural killer cell education in mice with single or multiple major histocompatibility complex class I molecules**
Sofia Johansson, Maria Johansson, Eleftheria Rosmaraki, Gustaf Vahlne, Ramit Mehr, Mali Salmon-Divon, François Lemonnier, Klas Kärre, and Petter Höglund

1157 **Type I interferon dependence of plasmacytoid dendritic cell activation and migration**
Carine Asselin-Paturel, Géraldine Brizard, Karine Chemin, Andre Boonstra, Anne O'Garra, Alain Vicari, and Giorgio Trinchieri

1169 **IL-1 receptor–associated kinase M is a central regulator of osteoclast differentiation and activation**
Hongmei Li, Esteban Cuartas, Weiguo Cui, Yongwon Choi, Todd D. Crawford, Hua Zhu Ke, Koichi S. Kobayashi, Richard A. Flavell, and Agnès Vignery
See news article on page 1023



Activation and migration of splenic plasmacytoid dendritic cells (red) in response to Toll-like receptor ligands depends on type I interferon.
See page 1157

IN THIS ISSUE

1180 Perfecting peptide priming
Prostate cancer's one-two punch
Healing with hyaluronan
Neutrophil–DC close encounters
Polymerase pinch hitters
Heather L. Van Epps

BRIEF DEFINITIVE REPORTS

1183 CD44 is a physiological E-selectin ligand on neutrophils
Yoshio Katayama, Andrés Hidalgo, Jungshan Chang, Anna Peired, and Paul S. Frenette

1191 Contribution of DNA polymerase η to immunoglobulin gene hypermutation in the mouse
Frédéric Delbos, Annie De Smet, Ahmad Faili, Said Aoufouchi, Jean-Claude Weill, and Claude-Agnès Reynaud
See news article on page 1181

1197 IL-7 receptor signaling is necessary for stage transition in adult B cell development through up-regulation of EBF
Kazu Kikuchi, Anne Y. Lai, Chia-Lin Hsu, and Motonari Kondo

ARTICLES

1205 Intestinal antiinflammatory effect of 5-aminosalicylic acid is dependent on peroxisome proliferator–activated receptor-γ
Christel Rousseaux, Bruno Lefebvre, Laurent Dubuquoy, Philippe Lefebvre, Olivier Romano, Johan Auwerx, Daniel Metzger, Walter Wahli, Béatrice Desvergne, Gian Carlo Naccari, Philippe Chavatte, Amaury Farce, Philippe Bulois, Antoine Cortot, Jean Frédéric Colombel, and Pierre Desreumaux

1217 Protection from angiotensin II–mediated vasculotoxic and hypertensive response in mice lacking PI3Kγ
Carmine Vecchione, Enrico Patrucco, Gennaro Marino, Laura Barberis, Roberta Poulet, Alessandra Aretini, Angelo Maffei, Maria Teresa Gentile, Marianna Storto, Ornella Azzolino, Mara Brancaccio, Gian Luca Colussi, Umberto Bettarini, Fiorella Altruda, Lorenzo Silengo, Guido Tarone, Mathias P. Wymann, Emilio Hirsch, and Giuseppe Lembo

1229 Among B cell non-Hodgkin's lymphomas, MALT lymphomas express a unique antibody repertoire with frequent rheumatoid factor reactivity
Richard J. Bende, Wilhelmina M. Aarts, Robert G. Riedl, Daphne de Jong, Steven T. Pals, and Carel J.M. van Noesel

JEM
THE JOURNAL OF EXPERIMENTAL MEDICINE
VOLUME 201 NUMBER 8
APRIL 18, 2005
www.jem.org

ON THE COVER
The image shows a smoothed domain structure of the MHC–TCR complex with a hole cut away to reveal the structure of a tumor-derived peptide. Related story by Chen et al.
See page 1243

1243 **Structural and kinetic basis for heightened immunogenicity of T cell vaccines**
Ji-Li Chen, Guillaume Stewart-Jones, Giovanna Bossi, Nikolai M. Lissin, Linda Wooldridge, Ed Man Lik Choi, Gerhard Held, P. Rod Dunbar, Robert M. Esnouf, Malkit Sami, Jonathan M. Boulter, Pierre Rizkallah, Christoph Renner, Andrew Sewell, P. Anton van der Merwe, Bent K. Jakobsen, Gillian Griffiths, E. Yvonne Jones, and Vincenzo Cerundolo
See news article on page 1180

1257 **Boosting antitumor responses of T lymphocytes infiltrating human prostate cancers**
Vincenzo Bronte, Tihana Kasic, Giorgia Gri, Keti Gallana, Giovanna Borsellino, Ilaria Marigo, Luca Battistini, Massimo Iafrate, Tommaso Prayer-Galetti, Francesco Pagano, and Antonella Viola
See news article on page 1180

1269 **γδ T cell–induced hyaluronan production by epithelial cells regulates inflammation**
Julie M. Jameson, Gabrielle Cauvi, Leslie L. Sharp, Deborah A. Witherden, and Wendy L. Havran
See news article on page 1181

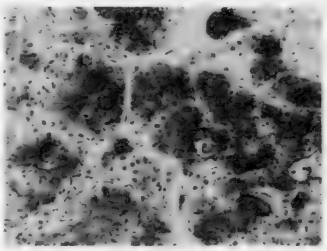
1281 **Neutrophils mediate immune modulation of dendritic cells through glycosylation-dependent interactions between Mac-1 and DC-SIGN**
Klaas P.J.M. van Gisbergen, Marta Sanchez-Hernandez, Teunis B.H. Geijtenbeek, and Yvette van Kooyk
See news article on page 1181

1293 **An anti-CD45RO/RB monoclonal antibody modulates T cell responses via induction of apoptosis and generation of regulatory T cells**
Silvia Gregori, Patrizia Mangia, Rosa Bacchetta, Eleonora Tresoldi, Frank Kolbinger, Catia Traversari, Josè M. Carballido, Jan E. de Vries, Ulf Korthäuer, and Maria-Grazia Roncarolo

1307 **Rapid mobilization of murine and human hematopoietic stem and progenitor cells with AMD3100, a CXCR4 antagonist**
Hal E. Broxmeyer, Christie M. Orschell, D. Wade Clapp, Giao Hangoc, Scott Cooper, P. Artur Plett, W. Conrad Liles, Xiaxin Li, Barbara Graham-Evans, Timothy B. Campbell, Gary Calandra, Gary Bridger, David C. Dale, and Edward F. Srour

1319 **Natural selection drives recurrent formation of activating killer cell immunoglobulin-like receptor and Ly49 from inhibitory homologues**
Laurent Abi-Rached and Peter Parham

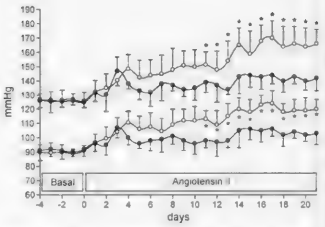
The antiinflammatory drug 5-aminosalicylic acid (green) exerts its effect by binding to the peroxisome proliferator–activator receptor–γ.
See page 1205



An anti-CD45 antibody induces regulatory T cells and prolongs the survival of insulin-producing (brown) human pancreatic islet cells in mice.
See page 1293

1333 Single cell analysis shows decreasing FoxP3 and TGFβ1 coexpressing $CD4^+CD25^+$ regulatory T cells during autoimmune diabetes
Shannon M. Pop, Carmen P. Wong, Donna A. Culton, Stephen H. Clarke, and Roland Tisch

1347 Correction



Heart rate in mice lacking the kinase PI3Kγ (filled circles) does not increase in response to the vasoactive peptide angiotensin II.
See page 1217

JEM
THE JOURNAL OF EXPERIMENTAL MEDICINE
VOLUME 201 NUMBER 9
MAY 2, 2005
www.jem.org

ON THE COVER
New advances in human subject research are featured in this issue. See editorial (page 1349), In This Issue (page 1352), and commentary (page 1355).

EDITORIAL

1349 Research on human subjects in the *JEM*
Ralph M. Steinman

FROM THE ARCHIVE

1351 Harry Goldblatt and the discovery of renin
Heather L. Van Epps

IN THIS ISSUE

1352 Exposing HIV
Relief from IL-1
Boosting innate immunity in cancer
Turning fat into muscle
Heather L. Van Epps

COMMENTARIES

1355 Blocking IL-1 in systemic inflammation
Charles A. Dinarello

BRIEF DEFINITIVE REPORTS

1361 Density of the Notch ligand Delta1 determines generation of B and T cell precursors from hematopoietic stem cells
Mari H. Dallas, Barbara Varnum-Finney, Colleen Delaney, Keizo Kato, and Irwin D. Bernstein

1367 T cell lineage choice and differentiation in the absence of the RNase III enzyme Dicer
Bradley S. Cobb, Tatyana B. Nesterova, Elizabeth Thompson, Arnulf Hertweck, Eric O'Connor, Jonathan Godwin, Christopher B. Wilson, Neil Brockdorff, Amanda G. Fisher, Stephen T. Smale, and Matthias Merkenschlager

ARTICLES

1375 Identification of proteoglycans as the APRIL-specific binding partners
Karine Ingold, Adrian Zumsteg, Aubry Tardivel, Bertrand Huard, Quynh-Giao Steiner, Teresa G. Cachero, Fang Qiang, Leonid Gorelik, Susan L. Kalled, Hans Acha-Orbea, Paul D. Rennert, Jürg Tschopp, and Pascal Schneider

1385 Differential requirement for OBF-1 during antibody-secreting cell differentiation
Lynn M. Corcoran, Jhagvaral Hasbold, Wendy Dietrich, Edwin Hawkins, Axel Kallies, Stephen L. Nutt, David M. Tarlinton, Patrick Matthias, and Philip D. Hodgkin

1397 **Transplantation of a multipotent cell population from human adipose tissue induces dystrophin expression in the immunocompetent mdx mouse**
Anne-Marie Rodriguez, Didier Pisani, Claude A. Dechesne, Claude Turc-Carel, Jean-Yves Kurzenne, Brigitte Wdziekonski, Albert Villageois, Claude Bagnis, Jean-Philippe Breittmayer, Hervé Groux, Gérard Ailhaud, and Christian Dani
See news article on page 1353

1407 **Antigenic conservation and immunogenicity of the HIV coreceptor binding site**
Julie M. Decker, Frederic Bibollet-Ruche, Xiping Wei, Shuyi Wang, David N. Levy, Wenquan Wang, Eric Delaporte, Martine Peeters, Cynthia A. Derdeyn, Susan Allen, Eric Hunter, Michael S. Saag, James A. Hoxie, Beatrice H. Hahn, Peter D. Kwong, James E. Robinson, and George M. Shaw
See news article on page 1352

1421 **A requirement for CD45 distinguishes Ly49D-mediated cytokine and chemokine production from killing in primary natural killer cells**
Nicholas D. Huntington, Yuekang Xu, Stephen L. Nutt, and David M. Tarlinton

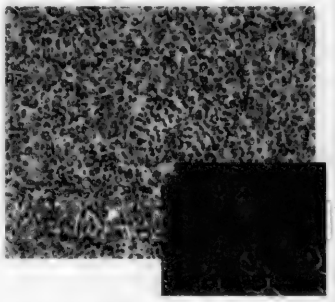
1435 **A type I interferon autocrine–paracrine loop is involved in Toll-like receptor-induced interleukin-12p70 secretion by dendritic cells**
Grégory Gautier, Martine Humbert, Florence Deauvieau, Mathieu Scuiller, John Hiscott, Elizabeth E.M. Bates, Giorgio Trinchieri, Christophe Caux, and Pierre Garrone

1447 **Differential requirements for the chemokine receptor CCR7 in T cell activation during *Listeria monocytogenes* infection**
Mischo Kursar, Uta E. Höpken, Markus Koch, Anne Köhler, Martin Lipp, Stefan H.E. Kaufmann, and Hans-Willi Mittrücker

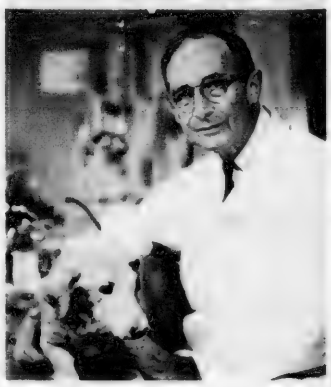
1459 **The 3′ end of the heavy chain constant region locus enhances germline transcription and switch recombination of the four γ genes**
Wesley A. Dunnick, Jian Shi, Kevin A. Graves, and John T. Collins

1467 **Intricate targeting of immunoglobulin somatic hypermutation maximizes the efficiency of affinity maturation**
Nai-Ying Zheng, Kenneth Wilson, Matthew Jared, and Patrick C. Wilson

1479 **Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade**
Virginia Pascual, Florence Allantaz, Edsel Arce, Marilynn Punaro, and Jacques Banchereau
See commentary on page 1355
See news article on page 1352



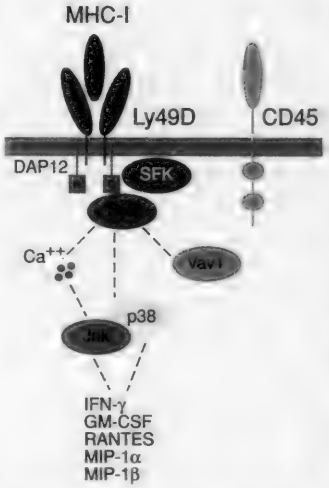
Elimination of the transcription factor PU.1 from adult hematopoietic cells enhances granulopoiesis.
See page 1487



Harry Goldblatt, who developed the first animal model of hypertension.
See page 1351

1487 PU.1 regulates the commitment of adult hematopoietic progenitors and restricts granulopoiesis
Aleksandar Dakic, Donald Metcalf, Ladina Di Rago, Sandra Mifsud, Li Wu, and Stephen L. Nutt

1503 Sustained expansion of NKT cells and antigen-specific T cells after injection of α-galactosyl-ceramide loaded mature dendritic cells in cancer patients
David H. Chang, Keren Osman, John Connolly, Anjli Kukreja, Joseph Krasovsky, Maggi Pack, Aisha Hutchinson, Matthew Geller, Nancy Liu, Rebecca Annable, Jennifer Shay, Kelly Kirchhoff, Nobusuke Nishi, Yoshitaka Ando, Kunihiko Hayashi, Hani Hassoun, Ralph M. Steinman, and Madhav V. Dhodapkar
See news article on page 1353



Cytokine and chemokine production by NK cells in response to Ly49D signaling requires the phosphatase CD45.
See page 1421

JEM
THE JOURNAL OF EXPERIMENTAL MEDICINE
VOLUME 201 NUMBER 10
MAY 16, 2005
www.jem.org

IN THIS ISSUE

1520 Protecting sight with F4/80
Fueling CD4$^+$ T cells
Deconstructing IκB kinase
Gut-grabbing T cells trigger GVHD
γδ T cells take on CMV
Heather L. Van Epps

BRIEF DEFINITIVE REPORTS

1523 Decay-accelerating factor modulates induction of T cell immunity
Peter S. Heeger, Peter N. Lalli, Feng Lin, Anna Valujskikh, Jinbo Liu, Nasima Muqim, Yuanyuan Xu, and M. Edward Medof

ARTICLES

1531 In vivo costimulatory role of B7-DC in tuning T helper cell 1 and cytotoxic T lymphocyte responses
Tahiro Shin, Kiyoshi Yoshimura, Takako Shin, Emily B. Crafton, Haruo Tsuchiya, Franck Housseau, Haruhiko Koseki, Richard D. Schulick, Lieping Chen, and Drew M. Pardoll

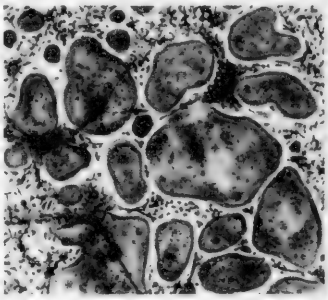
1543 A cytomegaloviral protein reveals a dual role for STAT2 in IFN-γ signaling and antiviral responses
Albert Zimmermann, Mirko Trilling, Markus Wagner, Manuel Wilborn, Ivan Bubic, Stipan Jonjic, Ulrich Koszinowski, and Hartmut Hengel

1555 Antigen persistence is required throughout the expansion phase of a CD4$^+$ T cell response
Reinhard Obst, Hisse-Martien van Santen, Diane Mathis, and Christophe Benoist
See news article on page 1520

1567 Shared reactivity of Vδ2^{neg} γδ T cells against cytomegalovirus-infected cells and tumor intestinal epithelial cells
Franck Halary, Vincent Pitard, Dorota Dlubek, Roman Krzysiek, Henri de la Salle, Pierre Merville, Claire Dromer, Dominique Emilie, Jean-François Moreau, and Julie Déchanet-Merville
See news article on page 1521

1579 Hematopoietic cells maintain hematopoietic fates upon entering the brain
Mei Massengale, Amy J. Wagers, Hannes Vogel, and Irving L. Weissman

1591 Recruitment of latent pools of high-avidity CD8$^+$ T cells to the antitumor immune response
Anne M. Ercolini, Brian H. Ladle, Elizabeth A. Manning, Lukas W. Pfannenstiel, Todd D. Armstrong, Jean-Pascal H. Machiels, Joan G. Bieler, Leisha A. Emens, R. Todd Reilly, and Elizabeth M. Jaffee



ON THE COVER
Image shows bone-resorbing osteoclasts, which are dependent on the β subunit of the IκB kinase complex for their development and survival. Related article by Ruocco et al.
See page 1677

1603 Generation of hematopoietic repopulating cells from human embryonic stem cells independent of ectopic *HOXB4* expression
Lisheng Wang, Pablo Menendez, Farbod Shojaei, Li Li, Frederick Mazurier, John E. Dick, Chantal Cerdan, Krysta Levac, and Mickie Bhatia

1615 The macrophage F4/80 receptor is required for the induction of antigen-specific efferent regulatory T cells in peripheral tolerance
Hsi-Hsien Lin, Douglas E. Faunce, Martin Stacey, Ania Terajewicz, Takahiko Nakamura, Jie Zhang-Hoover, Marilyn Kerley, Michael L. Mucenski, Siamon Gordon, and Joan Stein-Streilein
See news article on page 1520

1627 Fibrinogen and fibronectin binding cooperate for valve infection and invasion in *Staphylococcus aureus* experimental endocarditis
Yok-Ai Que, Jacques-Antoine Haefliger, Lionel Piroth, Patrice François, Eleonora Widmer, José M. Entenza, Bhanu Sinha, Mathias Herrmann, Patrick Francioli, Pierre Vaudaux, and Philippe Moreillon

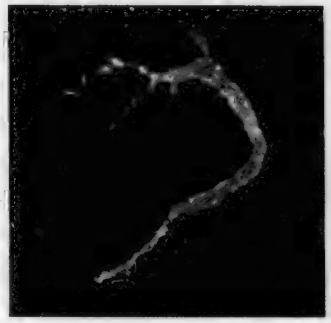
1637 Available carbon source influences the resistance of *Neisseria meningitidis* against complement
Rachel M. Exley, Jonathan Shaw, Eva Mowe, Yao-hui Sun, Nicholas P. West, Michael Williamson, Marina Botto, Harry Smith, and Christoph M. Tang

1647 TGF-β–dependent CD103 expression by $CD8^+$ T cells promotes selective destruction of the host intestinal epithelium during graft-versus-host disease
Riham El-Asady, Rongwen Yuan, Kechang Liu, Donghua Wang, Ronald E. Gress, Philip J. Lucas, Cinthia B. Drachenberg, and Gregg A. Hadley
See news article on page 1521

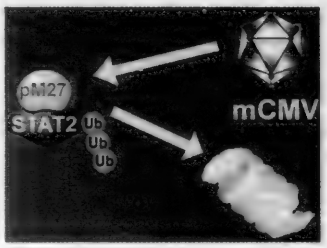
1659 Impaired early B cell tolerance in patients with rheumatoid arthritis
Jonathan Samuels, Yen-Shing Ng, Claire Coupillaud, Daniel Paget, and Eric Meffre

1669 Induction of vascular leakage through release of bradykinin and a novel kinin by cysteine proteinases from *Staphylococcus aureus*
Takahisa Imamura, Sumio Tanase, Grzegorz Szmyd, Andrzej Kozik, James Travis, and Jan Potempa

1677 IκB kinase (IKK)β, but not IKKα, is a critical mediator of osteoclast survival and is required for inflammation-induced bone loss
Maria Grazia Ruocco, Shin Maeda, Jin Mo Park, Toby Lawrence, Li-Chung Hsu, Yixue Cao, Georg Schett, Erwin F. Wagner, and Michael Karin
See news article on page 1520



GFP-expressing hematopoietic stem cells can differentiate into microglial cells (shown), but cannot transdifferentiate into neural cell types when transferred into irradiated recipients.
See page 1579



The murine cytomegalovirus protein M27 inhibits the signaling protein STAT2 resulting in impaired interferon-dependent antiviral gene expression.
See page 1543

IN THIS ISSUE

1690 Splicing for survival
Imaging tolerance
The mark of T reg cells
Brain-tethered T cells
Signaling commitment
Heather L. Van Epps

MEETING REVIEW

1693 *Mycobacterium tuberculosis* and the host response
Stefan H.E. Kaufmann, Stewart T. Cole, Valerie Mizrahi, Eric Rubin, and Carl Nathan

RETROSPECTIVE

1699 The career of Maclyn McCarty
Emil C. Gotschlich and Vincent A. Fischetti

COMMENTARIES

1709 Mutational escape from $CD8^+$ T cell immunity: HCV evolution, from chimpanzees to man
David G. Bowen and Christopher M. Walker

BRIEF DEFINITIVE REPORTS

1715 New insights on human T cell development by quantitative T cell receptor gene rearrangement studies and gene expression profiling
Willem A. Dik, Karin Pike-Overzet, Floor Weerkamp, Dick de Ridder, Edwin F. E. de Haas, Miranda R.M. Baert, Peter van der Spek, Esther E.L. Koster, Marcel J.T. Reinders, Jacques J.M. van Dongen, Anton W. Langerak, and Frank J.T. Staal

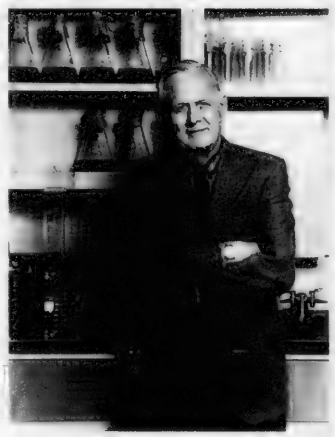
1725 Immune evasion versus recovery after acute hepatitis C virus infection from a shared source
Ian Tester, Susan Smyk-Pearson, Ping Wang, Anne Wertheimer, Ermei Yao, David M. Lewinsohn, John E. Tavis, and Hugo R. Rosen
See commentary on page 1709

1733 An essential role for SKAP-55 in LFA-1 clustering on T cells that cannot be substituted by SKAP-55R
Eun-Kyeong Jo, Hongyan Wang, and Christopher E. Rudd

JEM

THE
JOURNAL OF
EXPERIMENTAL
MEDICINE

VOLUME 201 NUMBER 11
JUNE 6, 2005
www.jem.org



ON THE COVER
In this issue, Emil C. Gotschlich and Vincent A. Fischetti provide a retrospective of the career of their colleague, mentor and friend Maclyn McCarty, a long-time *JEM* Editor who passed away earlier this year. Photo of McCarty in his lab in 1983 provided by the Rockefeller University Archive.
See page 1699

ARTICLES

1741 **Cellular immune selection with hepatitis C virus persistence in humans**
Andrea L. Cox, Timothy Mosbruger, Qing Mao, Zhi Liu, Xiao-Hong Wang, Hung-Chih Yang, John Sidney, Alessandro Sette, Drew Pardoll, David L. Thomas, and Stuart C. Ray
See commentary on page 1709

1753 **Divergent and convergent evolution after a common-source outbreak of hepatitis C virus**
Stuart C. Ray, Liam Fanning, Xiao-Hong Wang, Dale M. Netski, Elizabeth Kenny-Walsh, and David L. Thomas
See commentary on page 1709

1761 **Recruitment of Gr-1$^+$ monocytes is essential for control of acute toxoplasmosis**
Paul M. Robben, Marie LaRegina, William A. Kuziel, and L. David Sibley

1771 **Inflammation and the reciprocal production of granulocytes and lymphocytes in bone marrow**
Yoshihiro Ueda, Motonari Kondo, and Garnett Kelsoe

1781 **Osteopontin is a hematopoietic stem cell niche component that negatively regulates stem cell pool size**
Sebastian Stier, Yon Ko, Randolf Forkert, Christoph Lutz, Thomas Neuhaus, Elisabeth Grünewald, Tao Cheng, David Dombkowski, Laura M. Calvi, Susan R. Rittling, and David T. Scadden

1793 **Coexpression of CD25 and CD27 identifies FoxP3$^+$ regulatory T cells in inflamed synovia**
Claudia R. Ruprecht, Marco Gattorno, Francesca Ferlito, Andrea Gregorio, Alberto Martini, Antonio Lanzavecchia, and Federica Sallusto
See news item on page 1691

1805 **Live imaging of effector cell trafficking and autoantigen recognition within the unfolding autoimmune encephalomyelitis lesion**
Naoto Kawakami, U. Valentin Nägerl, Francesca Odoardi, Tobias Bonhoeffer, Hartmut Wekerle, and Alexander Flügel
See news item on page 1691

1815 **In situ characterization of CD4$^+$ T cell behavior in mucosal and systemic lymphoid tissues during the induction of oral priming and tolerance**
Bernd H. Zinselmeyer, John Dempster, Alison M. Gurney, David Wokosin, Mark Miller, Hsiang Ho, Owain R. Millington, Karen M. Smith, Catherine M. Rush, Ian Parker, Michael Cahalan, James M. Brewer, and Paul Garside
See news item on page 1690

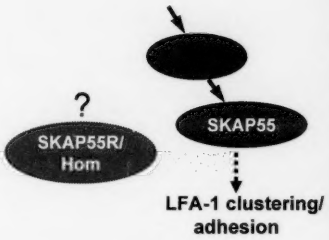
Three articles and a commentary in this issue explore hepatitis C virus evolution and immune escape during human infections.
See pages 1709, 1725, 1741, and 1753

The lymphoid (B220$^+$) and granulocyte (Gr-1$^+$) bone marrow compartments share a developmental niche that excludes the erythroid (TER119$^+$) lineages.
See page 1771

1825 Histone deacetylase activity is essential for the expression of *HoxA9* and for endothelial commitment of progenitor cells
Lothar Rössig, Carmen Urbich, Thomas Brühl, Elisabeth Dernbach, Christopher Heeschen, Emmanouil Chavakis, Ken-ichiro Sasaki, Diana Aicher, Florian Diehl, Florian Seeger, Michael Potente, Alexandra Aicher, Lucia Zanetta, Elisabetta Dejana, Andreas M. Zeiher, and Stefanie Dimmeler
See news item on page 1691

1837 Mimicry of a constitutively active pre–B cell receptor in acute lymphoblastic leukemia cells
Niklas Feldhahn, Florian Klein, Jana L. Mooster, Paul Hadweh, Mieke Sprangers, Maria Wartenberg, Mohamed M. Bekhite, Wolf-Karsten Hofmann, Sebastian Herzog, Hassan Jumaa, Janet D. Rowley, and Markus Müschen
See news item on page 1690

1853 SURFIN is a polymorphic antigen expressed on *Plasmodium falciparum* merozoites and infected erythrocytes
Gerhard Winter, Satoru Kawai, Malin Haeggström, Osamu Kaneko, Anne von Euler, Shin-ichiro Kawazu, Daniel Palm, Victor Fernandez, and Mats Wahlgren



The adaptor SKAP-55, but not the closely related SKAP-55R, is essential for "inside-out signaling" that couples the T cell receptor to integrin clustering.
See page 1733

IN THIS ISSUE

1866 Deadly stowaway
C4BP runs damage control
Indecisive interleukin-4?
Lymphocytes that can't let go
Heather L. Van Epps

COMMENTARIES

1869 No audible wheezing: nuggets and conundrums from mouse asthma models
Joshua A. Boyce and K. Frank Austen
See commentary on page 1875

1875 Nonhuman primate models of asthma
Robert L. Coffman and Edith M. Hessel
See commentary on page 1869

1881 Antiviral T cell responses: phalanx or multipronged attack?
David N. Posnett, Manuel E. Engelhorn, Alan N. Houghton

BRIEF DEFINITIVE REPORTS

1885 Shifts in targeting of class switch recombination sites in mice that lack μ switch region tandem repeats or Msh2
Irene M. Min, Lisa R. Rothlein, Carol E. Schrader, Janet Stavnezer, and Erik Selsing

1891 Identification of eosinophil lineage–committed progenitors in the murine bone marrow
Hiromi Iwasaki, Shin-ichi Mizuno, Robin Mayfield, Hirokazu Shigematsu, Yojiro Arinobu, Brian Seed, Michael F. Gurish, Kiyoshi Takatsu, and Koichi Akashi

1899 Interleukin (IL)-4 inhibits IL-10 to promote IL-12 production by dendritic cells
Yongxue Yao, Wei Li, Mark H. Kaplan, and Cheong-Hee Chang
See news item on page 1867

ARTICLES

1905 A chromosomally integrated bacteriophage in invasive meningococci
Emmanuelle Bille, Jean-Ralph Zahar, Agnes Perrin, Sandrine Morelle, Paula Kriz, Keith A. Jolley, Martin C.J. Maiden, Catherine Dervin, Xavier Nassif, and Colin R. Tinsley
See news item on page 1866

JEM

THE JOURNAL OF EXPERIMENTAL MEDICINE

VOLUME 201 NUMBER 12
JUNE 20, 2005
www.jem.org

ON THE COVER
Pen and ink drawing by New York sculptor and artist Sammy Shin (shinart@yahoo.com). Two commentaries in this issue discuss the use of mice and monkeys to model asthma. See pages 1869 and 1875

1915 **Properties and protective value of the secondary versus primary T helper type 1 response to airborne *Mycobacterium tuberculosis* infection in mice**
Yu-Jin Jung, Lynn Ryan, Ronald LaCourse, and Robert J. North

1925 **IFN-γ production by alloantigen-reactive regulatory T cells is important for their regulatory function in vivo**
Birgit Sawitzki, Cherry I. Kingsley, Vanessa Oliveira, Mahzuz Karim, Manuela Herber, and Kathryn J. Wood

1937 **C4b-binding protein binds to necrotic cells and DNA, limiting DNA release and inhibiting complement activation**
Leendert A. Trouw, Sara C. Nilsson, Isabel Gonçalves, Göran Landberg, and Anna M. Blom
See news item on page 1866

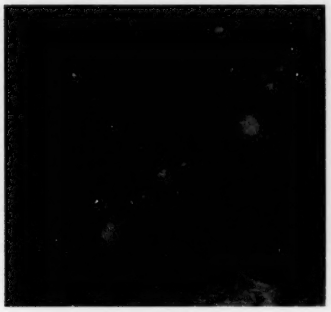
1949 **Combined loss of proapoptotic genes Bak or Bax with Bim synergizes to cause defects in hematopoiesis and in thymocyte apoptosis**
Jack Hutcheson, John C. Scatizzi, Emily Bickel, Nathaniel J. Brown, Philippe Bouillet, Andreas Strasser, and Harris Perlman

1961 **Leukotriene B_4, an activation product of mast cells, is a chemoattractant for their progenitors**
Charlotte L. Weller, Sarah J. Collington, Jeremy K. Brown, Hugh R.P. Miller, Adam Al-Kashi, Peter Clark, Peter J. Jose, Adele Hartnell, and Timothy J. Williams

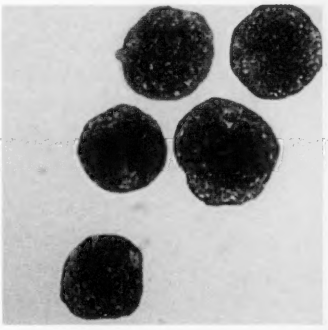
1973 **Sequential activation of NKT cells and NK cells provides effective innate immunotherapy of cancer**
Mark J. Smyth, Morgan E. Wallace, Stephen L. Nutt, Hideo Yagita, Dale I. Godfrey, and Yoshihiro Hayakawa

1987 **Importance of integrin LFA-1 deactivation for the generation of immune responses**
Monika Semmrich, Andrew Smith, Carolin Feterowski, Sandra Beer, Britta Engelhardt, Dirk H. Busch, Bernadett Bartsch, Melanie Laschinger, Nancy Hogg, Klaus Pfeffer, and Bernhard Holzmann
See news item on page 1867

1999 **Repertoire, diversity, and differentiation of specific CD8 T cells are associated with immune protection against human cytomegalovirus disease**
Karim Sacre, Guislaine Carcelain, Nathalie Cassoux, Anne-Marie Fillet, Dominique Costagliola, Daniel Vittecoq, Dominique Salmon, Zahir Amoura, Christine Katlama, and Brigitte Autran
See commentary on page 1881



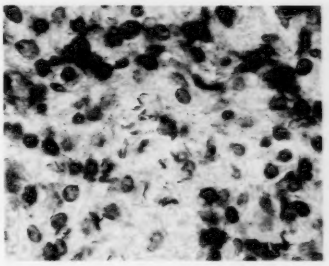
Bone marrow–derived mast cells (green) migrate out of capillaries (red) and accumulate at sites of intradermal leukotriene B_4 injection.
See page 1961



Eosinophil-committed precursors are derived exclusively from a fraction of granulocyte/monocyte progenitor cells that activate the transcription factor GATA-1.
See page 1891

2011 **B cells from hyper-IgM patients carrying *UNG* mutations lack ability to remove uracil from ssDNA and have elevated genomic uracil**
Bodil Kavli, Sonja Andersen, Marit Otterlei, Nina B. Liabakk, Kohsuke Imai, Alain Fischer, Anne Durandy, Hans E. Krokan, and Geir Slupphaug

2023 **Myeloid and plasmacytoid dendritic cells transfer HIV-1 preferentially to antigen-specific $CD4^+$ T cells**
Karin Loré, Anna Smed-Sörensen, Jayanand Vasudevan, John R. Mascola, and Richard A. Koup



Immunization of mice with live *Mycobacterium tuberculosis* results in an earlier accumulation of $CD4^+$ T cells (brown) in lungs but does not result in resolution of a secondary infection.
See page 1915